Editor's Choice

Cavity-promoted Diels–Alder Reactions of Unsubstituted Naphthalene: Fine Reactivity Tuning by Cavity Shrinkage[#]

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By finely tuning the cavity volume of a coordination cage, the Diels–Alder reactivity of aromatic compounds was enhanced. Even unsubstituted naphthalene could be made to undergo the Diels–Alder reaction with *N-tert*-butylmaleimide, with perfectly controlled syn-selectivity. M_6L_4 cages with standard and contracted cavities had opposite effects on the reaction: the former favored larger Diels–Alder substrates, whereas the latter favored smaller ones.

Well-defined cage cavities can activate otherwise inert substrates to accelerate chemical reactions with high regio- and stereoselectivity.¹ The close proximity of the substrates' reaction sites in the cavity is indispensable, and fine tuning of substrate structures is often required to achieve highly efficient reactions. In our previous studies on the Diels–Alder reactions of aromatic compounds within M_6L_4 cage **1b** (Figure 1),² unnecessary alkyl substituents had to be introduced into the substrate to enhance their reactivity.^{2c} Here, we report that the substrate reactivity can be changed dramatically without modifying the substrate structures but by finely tuning the cavity volume of cage **1**.

Recently, we have shown that the effective cavity volume of cage **1** is easily contracted by functionalizing the 1,10phenanthroline ancillary ligand on the Pd(II) units with sterically demanding groups.³ The cavity volume is, in particular, significantly reduced (by as much as ca. 20%) with mesityl (Mes) group functionalization (Figure 1).⁴ Contracted cage **1a** showed binding behavior different from that of **1b** toward large organic guests, but we have not previously examined the effect of the cavity contraction on reactivity control. Here, we show



Figure 1. Self-assembled coordination cages **1**. The cavity volume of **1** shown in parentheses was calculated based on each X-ray crystal structure using the *VOIDOO* program (probe radius: 3.36 Å). For details, see ref 3.



Scheme 1. Cavity-promoted Diels–Alder reactions of naphthalene 2 with *N*-alkyl maleimide 3.

that in the contracted cavity, even unsubstituted naphthalene smoothly undergoes the Diels–Alder reaction, and suggest a catalytic cycle for the reaction (Scheme 1).⁵

Expecting enhanced reactivity for the Diels-Alder reaction, unsubstituted naphthalene 2a (20 µmol), which was inert in cage 1b,^{2c} was treated with *N*-tert-butylmaleimide (3a, 10 µmol) in an aqueous solution of cage 1a (1.0 mM, 10.0 mL, 10 µmol) at 80 °C.6 Unlike its inclusion in cage 1b, in which a ternary complex [namely, $1b \cdot (2a \cdot 3a)$] is easily formed, after 1 h stirring, contracted cage 1a bound only one molecule of 2a to form inclusion complex 1a.2a in 60% vield. Maleimide 3a. though slightly soluble in water, remained largely unbound and suspended in the reaction solution. A small portion of dissolved 3a may have formed ternary complex $1a \cdot (2a \cdot 3a)$, as the signals of 3a were slightly shifted upfield ($\Delta \delta = -0.24$ ppm for the olefin protons). When this mixture was heated at 100 °C for 24 h, however, the pale yellow solution turned cloudy. In a control experiment in D_2O , a new set of signals appeared in the ¹H NMR spectrum at this stage, strongly indicating that the Diels-Alder reaction started to occur at 100 °C. The reaction mixture was filtered, and the filtrate was extracted with chloroform. ¹H NMR spectroscopy of the filtrate showed the formation of Diels-Alder product 4a. The filtered solid also included 4a as a major component. The combined crude product was purified by column chromatography and gel permeation chromatography to give pure 4a in 46% isolated yield. When the reaction was carried out at 110 °C, the yield was increased to 58%.

The syn stereochemistry of **4a** was deduced from the upfield-shifted *N-tert*-butyl protons ($\delta = 1.17$ ppm), which are located above the benzene ring. An NOE correlation between the vinyl protons and the bridgehead protons also supported the stereochemistry. No anti isomer was detected by NMR spectroscopy. With the sterically unbiased cage **1b**, **2a**, and **3a** were coencapsulated to give ternary complex **1b** (**2a** · **3a**) in 71%



Scheme 2. Equilibrium of ternary complex $1a \cdot (2a \cdot 3a)$ with inclusion complex $1a \cdot 2a$ and free 3a.

yield, but no Diels–Alder products were formed after heating the inclusion complex at 100 °C. We thus presume that ternary complex $1a \cdot (2a \cdot 3a)$, which is indispensable for the formation of 4a, is in equilibrium with inclusion complex $1a \cdot 2a$ and free 3a. Though the equilibrium is much in favor of $1a \cdot 2a$ (Scheme 2), the tightly preorganized $2a \cdot 3a$ pair in the minor $1a \cdot (2a \cdot 3a)$ component rapidly undergoes the reaction at 100– 110 °C.

It is noteworthy that subtle changes in the Diels–Alder substrate or cavity volume result in large differences in the reactivity. The total volume of 2a + 3a (315 Å³) seems to be the best fit for cage 1a, allowing a tight fit and close proximity of the reaction sites, thus giving the highest yield of adduct 4a. With increasing volume, the substrate pairs were not well accommodated or no longer fit in the cavity, and the yields of the products decreased significantly (Table 1). In contrast, the guest pair 2a + 3a is loosely bound in the cavity of standard cage 1b and no reaction takes place. The Diels–Alder reaction occurs in 1b only when substrates are modified with alkyl substituents, so they can be tightly bound in the larger cavity (see the formation of 4e and 4f in Table 1).

We also note that product **4a** was released to some extent from the cavity of **1a** under the reaction conditions. The spontaneous product release is a crucial step for accomplishing a catalytic cycle for the reaction (Figure 2). Thus, the reaction of **2a** and **3a** was examined with a catalytic amount (5 mol %) of cage **1a**. The mixture of **2a** (50 µmol) and maleimide **3a** (50 µmol) was suspended in an aqueous solution of **1a** (0.25 mM, 10.0 mL, 2.5 µmol) and stirred at 110 °C for 48 h. From the reaction mixture, Diels–Alder product **4a** was isolated in 33% yield; this corresponds to a turnover number (TON) of 6.6 based on cage catalyst **1a**. The reaction was very slow but did proceed catalytically at 110 °C.

The fine tuning of the cavity volume is also effective for the activation of other inert aromatics. For example, the Diels–Alder reaction of triphenylene **5** with maleimide **3a** proceeded to give adduct **6** in only 40% yield within cage **1b** but in 75% yield within cage **1a**. This is presumably because the substrate pair was more closely packed in the contracted cavity of **1a** (Scheme 3).^{2b} The ¹H NMR spectrum of inclusion complex **1a**•**6** showed a severe splitting pattern of the host signals, revealing strong host–guest interactions. Thus, the catalytic cycle was hampered by product inhibition.

In summary, we succeeded in performing the Diels–Alder reaction of unsubstituted naphthalene by shrinking the cavity of a self-assembled M_6L_4 cage. Previously, the only way to achieve preorganized orientation of substrates in this cavity had been through the introduction of substituents onto the substrates themselves. We now have another option: the cage cavity can be homogeneously deformed and contracted by functionalizing the

 Table 1. Isolated yields of Diels-Alder adducts 4 generated in the standard (1a) and contracted (1b) cavities^a

Substrate	Product (Volume ^b /Å ³)		Yield of 4 ^c /%	
(Volume ^b /Å ³)			With 1a	With 1b
2a + 3a (315) 151 + 164	N NO	4a (293)	46 (58) ^d ()
2b + 3a (351) 187 + 164	° ×	4b (332)	35	0
2c + 3a (387) 223 + 164	° ×	4c (368)	29	0
2a + 3b (340) 151 + 189	N N N	4d (317)	0	0
2b + 3b (376) 187 + 189	N NO	4e (357)	0	5
2c + 3b (412) 223 + 189	P N O	4f (374)	0	43

^aReaction conditions: cage **1** (10 µmol), naphthalene **2** (20 µmol), and maleimide **3** (10 µmol) in D₂O (10.0 mL) at 100 °C for 24 h. ^bvan der Waals volumes calculated from structures optimized using SPARTAN'10 with MP2 using a 6-31G* basis set. °Isolated yields. ^dIsolated yield in the reaction at 110 °C.



Figure 2. Proposed mechanism for the catalytic Diels-Alder reaction of naphthalene 2a with maleimide 3a in the presence of cage 1a.



Scheme 3. Cavity-promoted Diels–Alder reaction of triphenylene 5 with *N-tert*-butylmaleimide 3a.

outer pendant groups of the cage. Because the cage cavity gradually shrinks as the bulkiness of the substituents of the phenanthroline ancillary ligand increases,^{3b} a variety of substrate pairs can, in principle, be accommodated and reacted within the M_6L_4 cage without modifying the substrates themselves. We believe that the present method expands the possibilities for and the effectiveness of cavity-directed reactions.

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Supporting Information is available electronically on J-STAGE.

References and Notes

- # Dedicated to Professor Iwao Ojima on the occasion of his 70th birthday.
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- 6 Because unsubstituted naphthalene **2a** easily sublimes even at room temperature, an excess amount of **2a** was used.